PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	25 MAR 2009
Applicant's or agent's file reference DMB-4112-78	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 08/12440	31 October 2008 (31.10.2008)	31 October 2007 (31.10.2007)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 47/00 (2009.01)
USPC - 514/789

Applicant DIFFUSION PHARMACEUTICALS LLC

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	08 March 2009 (08.03.2009)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:
   - [x] the international application in the language in which it was filed.
   - [ ] a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. [ ] This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:

   a. type of material
      - [ ] a sequence listing
      - [ ] table(s) related to the sequence listing

   b. format of material
      - [ ] on paper
      - [ ] in electronic form

   c. time of filing/furnishing
      - [ ] contained in the international application as filed
      - [ ] filed together with the international application in electronic form
      - [ ] furnished subsequently to this Authority for the purposes of search

4. [ ] In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the appicable time limit:

   ☐ paid additional fees

   ☐ paid additional fees under protest and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☒ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: claims 1-7, directed to a pharmaceutical composition comprising a diffusion enhancing compound.
Group II: claims 8, 10, 11, and 19-21, directed to a method for enhancing the diffusion of oxygen in a mammal and treating respiratory deficiencies or diseases using said enhanced diffusion of oxygen comprising administering a diffusion enhancing compound
Group III: claims 9, and 19-21, directed to a method of treating hemorrhagic shock comprising administering a diffusion enhancing compound.
Group IV: claims 12, 17 and 19-21, directed to a method of treating myocardial infarction, hypertension, ischemia or stroke comprising administering a diffusion enhancing compound.
Group V: claims 13 and 19-21, directed to a method of treating traumatic brain injury or Alzheimer's disease comprising administering a diffusion enhancing compound.
Group VI: claims 14 and 19-21, directed to a method of treating anemia comprising administering a diffusion enhancing compound.
Group VII: claims 15 and 19-21, directed to a method of treating chronic renal failure comprising administering a diffusion enhancing compound.
Group VIII: claims 16, 19-21, 23, 25 and 26, directed to a method of treating cancer comprising administering a diffusion enhancing compound.
Group IX: claims 18-21, directed to a method of treating diabetes and diabetes related complications comprising administering a diffusion enhancing compound.
Group X: claims 22, 25 and 26, directed to a method of treating Wegener's granulomatosis comprising administering a diffusion enhancing compound.
Group XI: claims 24-26, directed to a method of treating arthritis comprising administering a diffusion enhancing compound.

The inventions listed as Groups I - XI do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The special technical feature of the Group I claims is a pharmaceutical composition comprising a diffusion enhancing compound. The special technical feature of the Group II-XI claims is the use of a preparation comprising a diffusion enhancing compound to treat a variety of individual diseases or conditions.

The only common technical element shared by the above groups is that they are related to the use of a diffusion enhancer in a pharmaceutical preparation. This common technical element does not represent an improvement over the prior art of the article entitled "Synergistic Effects of Chemical Enhancers and Therapeutic Ultrasound on Transdermal Drug Delivery" by Johnson et al. (see abstract). Therefore, the inventions of Groups I-XI lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.

4. Consequently, this opinion has been established in respect of the following parts of the international application:

   ☐ all parts

   ☒ the parts relating to claims Nos. 1-7

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Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	4-6	YES
	Claims	1-3 and 7	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1-7	NO
Industrial applicability (IA)	Claims	1-7	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims 1-3 and 7 lack novelty under PCT Article 33 (2) as being anticipated by the article entitled "synergistic effects of chemical enhancers and therapeutic ultrasound on transdermal drug delivery" by Johnson et al. (hereafter "Johnson").

Regarding claim 1, Johnson teaches a pharmaceutical composition comprising a diffusion enhancing compound and a pharmaceutically acceptable carrier (abstract).

Regarding claim 2, Johnson teaches the pharmaceutical composition comprising a unit dose of a diffusion enhancing compound and a pharmaceutically acceptable carrier (abstract; table 1)

Regarding claim 3, Johnson teaches the pharmaceutical composition as in claim 1 wherein the diffusion enhancing compound is selected from glycerol (abstract; table 2).

Regarding claim 7, Johnson teaches the pharmaceutical composition wherein the pharmaceutically acceptable carrier is PEG (table 2-3).

Claims 4-6 lack an inventive step under PCT Article 33 (3) as being obvious over Johnson in view of US 2007/0088248 A1 to Glenn et al. (hereater 'Glenn').

Regarding claim 4, Johnson does not teach the pharmaceutical composition as in claim I wherein the diffusion enhancing compound is trehalose. However, Glenn teaches the pharmaceutical composition wherein the diffusion enhancing compound is trehalose (para [0156]). It would have been obvious to one of skill in the art to incorporate trehalose as taught by Glenn in to the diffusion enhancing formulation as taught by Johnson in order to obtain a stable formulation (para [0157], non-reducing saccharide).

Regarding claim 5, Glenn teaches the pharmaceutical composition wherein the small or multiply-charged ion with high charge density is SO.sub.4 (para [0156]).

Regarding claim 6, Glenn teaches the pharmaceutical composition wherein the composition is an aqueous based solution (para [0135]).

Claims 1-7 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.